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10/644,288	08/20/2003	Paul Diamond	PT100-3	5798

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EXAMINER

POPA, ILEANA

ART UNIT PAPER NUMBER

1633

DATE MAILED: 02/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

10/644,288

Applicant(s)

DIAMOND, PAUL

Examiner

Ileana Popa

Art Unit

1633

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 06 January 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 17-36 is/are pending in the application.
- 4a) Of the above claim(s) 21,23,26,28,31 and 33-35 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 17-20,22,24,25,27,29,30,32 and 36 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_

### DETAILED ACTION

1. Applicant's election of Group II(iii) drawn to a method for excising a pre-selected DNA sequence from the cellular genome in response to the presence of a viral RNA molecule that has at least one region of predetermined sequence, (claims 17-20, 22, and 24) is acknowledged. Election was made with traverse in the reply filed on 10/27/2005.

The traversal is on the grounds that the restriction requirement between Group II(iii) and Group III are not independent. Applicant asserts that the method and the cell of the invention of Group III are a special case of the corresponding generic claims of the invention of Group II(iii), and the invention of Group III cannot be practiced without practicing the invention of Group II(iii). This is found persuasive and the restriction requirement between the inventions of Groups II and III is withdrawn.

Applicant's election of species of constitutively active promoter (claim 32) and transgenic plant (claim 36), which species belong to the rejoined invention of Group III, is also acknowledged.

Applicant has consented to the withdrawal of claims 1-16. Additionally, claims 21, 23, 26, 28, 31, and 33-35 have been withdrawn from further consideration as being drawn to non-elected species.

The linking claim 22 present in Groups II(i) and II(iii) will be examined in light of their broadest, reasonable interpretation.

Claims 17-20, 22, 24, 25, 27, 29, 30, 32, and 36 are pending.

***Claim Rejections - 35 USC § 101***

2. 35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

3. Claims 18-20, 22, 29, 30, and 32 are rejected under 35 USC §101 because the claimed invention is directed to non-statutory subject matter. The term "cell" is not defined by the specification. In the absence of the contrary, the cell is present or intended to be present in a human being, said cell becoming integrated into the human being and therefore being an inseparable part of the human itself. Similarly, the term "multi-cellular organism" reads on a human being. The scope of the claims, therefore, encompasses a human being, which is non-statutory subject matter. As such, the recitation of the limitation "non-human" would be remedial. See 1077 O.G. 24, April 21, 1987.

***Claim Rejections - 35 USC § 112 - enablement***

4. Claims 17-20, 22, 24, 25, 27, 29, 30, 32, and 36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make or use the claimed invention, if not, whether an artisan would require undue

experimentation to make and use the claimed invention and whether working examples have been provided.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC § 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

*Wands* states on page 1404,  
“Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skills of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.”

### **The Breadth of the Claims**

The instant claims 17-20, 22, 24, 25, 27, 29, 30, 32, and 36 are drawn to (i) a method for selectively excising a pre-selected DNA sequence from a cellular genome and to a cell or multi-cellular organism wherein a pre-selected DNA sequence is excisable from the genome (claims 17-20, 22, and 24) and (ii) a method for bringing the expression of a pre-selected gene in a cell under the control of a pre-selected promoter and to a cell or multi-cellular organism wherein the expression of a pre-selected gene can be brought under the control of a pre-selected promoter (claims 25, 27, 29, 30, 32, and 36).

The aspects considered broad are the (i) the cell to be genetically modified, (ii) the multi-cellular organism to be genetically modified, and (iii) the polynucleic acid molecule having at least one region of predetermined sequence. As will be shown below, these broad aspects are not enabled for their embraced full scope.

### **The Nature of the Invention**

The nature of the invention is method to introduce genetic modifications into a cell or multi-cellular organism such that the selective excision of a pre-selected DNA sequence is achieved. Such invention has use in the art for making viral-resistant multi-cellular organisms or multi-cellular organisms capable to report viral infection.

Applicant contemplates to selectively excise a pre-selected DNA sequence from the cellular genome by providing a cell with: (i) an excisable sequence element bounded on either side by specific excision sequences, (ii) a repressible promoter operably linked to a gene encoding a site-specific recombinase, (iii) a gene encoding a repressor protein specific for the repressible promoter and (iv) means of RNA silencing against the mRNA encoding the repressor protein in response to the presence in the cell of a polynucleic acid molecule having a region of predetermined sequence so that the site-specific recombinase is expressed causing elimination from the genome of the excisable sequence element.

Therefore, the nature of the invention is within the broad genera of gene targeting and gene targeting does not generally enable Applicant's invention due to problems with the complexity and unpredictability of such methods. Kolb et al. (Trends in Biotechnology, 2005, 23: 399-406) teach:

"Gene repair and targeted integration strategies hold significant promise for both gene therapy and animal transgenesis. However, several technical difficulties still need to be addressed. The frequencies of modification achieved in different cell lines vary widely and several factors are responsible for this variance. First, the cell cycle, the metabolic state of the cell, the capacity of the cell to be transformed with the corrective agent and the inherent activity of DNA repair pathways are parameters that need to be defined for the cell type in which gene modification is envisioned. A particular methodology might be highly suitable for some genome modification approaches but not for others. Second, the modification reaction might be affected by the transcriptional state of the targeted

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gene and the replication activity around the targeted region. Such parameters could define whether the transcribed or non-transcribed, lagging or leading strands are more accessible or amenable to gene repair. Transcriptional activity and replication status also correlate with chromatin structure, which can sterically preclude the corrective agent from locating the target.”

Hence, from the nature of the invention, the Artisan would not reasonably predict that the any cell or multi-cellular organism genetically modified as claimed could be used to regulate gene expression as a result of the presence of a polynucleic acid molecule having a region of predetermined sequence.

#### **The State of the Prior Art and the Level of Predictability in the Art/Amount of Experimentation Necessary**

The issue is whether or not such a claimed regulation of gene expression could have been practiced by a person skilled in the art without undue experimentation, at the time the invention was made.

As mentioned above, the applicant contemplates regulating cellular gene expression by genetically modifying cells or multi-cellular organisms such that they can excise preselected DNA sequences from their genome as a result of the presence of a polynucleic acid molecule that causes RNA silencing against the repressor protein that controls the expression of the site-specific recombinase.

In order for this methodology to work, the above-mentioned series of DNA sequences must integrate into the cell genome. This can take place by two main processes: transfection or homologous recombination.

In case transfection is used, how would one of skill in the art know to transfect the foreign DNA such that the encoded product is efficiently expressed (i.e., avoiding

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the chromosomal positional effects that adversely affect expression), without disturbing expression of essential genes? Introduction of transgene into cells is inefficient and can be accompanied by potentially mutagenic random integration into the genome; alternately, random insertion can lead to inefficient expression. For example, in their review article, Coates et al. (Trends in Biotechnology, 2005, 23: 407-419) teach:

“Foreign DNA can be transported into eukaryotic cells by physical, chemical or biological methods (e.g., microinjection, liposomes, electroporation, gene-gun or viral vectors). Stable integration of the foreign DNA will only occur in a small proportion of the cells that have taken up the DNA. Integration of the foreign DNA is mediated by the cellular DNA repair enzymes and occurs at random sites of the genome. If the foreign DNA contains sequences that are identical to the host genome, it might be inserted by homologous recombination in a small fraction of the transduced cells.

The integration at random sites often places the transgene into an environment that is not supportive of its expression.”

With respect to the random insertion, Wurtele et al. (Gene Therapy, 2003, 10: 1791-1799, Review) teach:

“Many transfection procedures have been developed that enable DNA to enter the cytoplasm, but its passage into nucleus is mainly mediated by cellular processes. After its entry into the nucleus, a large proportion of the foreign DNA is rapidly degraded and diluted among subsequent divisions.

[I]n approximately one cell per thousand, the introduced foreign DNA will integrate into chromosomal DNA.

[I]llegitimate integration is typically 1000-10000 more frequent than the targeted integration. These mechanisms give rise to much less predictable integrated structures, as one cannot preselect the genomic site of integration, nor the resulting foreign DNA chromosome structure. The conditions governing how the cell chooses which mode of integration to employ are unclear.

It must therefore be stressed that DNA often integrates into the genome in ways that we do not fully understand, nor totally control.

Some integration events are relatively “harmless” to the integrity of the genomic site and can sometimes leave the recipient locus completely unchanged (apart from the inclusion of the new sequence). However, more complex insertion patterns are frequently observed. The recipient genomic locus can undergo extensive physical rearrangements



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at the site of integration, including deletions (as much as tens of kb), duplications, and translocations among others. Another consequence is that the integrated material can interrupt coding sequences.

Aside from physical rearrangements, illegitimate DNA integration can alter other cellular characteristics, such as perturbation of genome-wide methylation patterns. The mechanisms involved are not fully understood, but the consequences for the recipient genome can be drastic. Since gene expression levels can be modified by promoter methylation, the integration of foreign DNA can give rise to diverse phenotypes.

Thus, illegitimate integration events can have dramatic repercussions on the content, organization, and the functions of the recipient genome."

By contrast, homologous recombination provides a precise mechanism for targeting defined modifications to genomes in living cells. However, at the time the invention was made, and even in the present, the technology was presented with difficulties and the outcome was unpredictable. With respect to homologous recombination in mammals, Vasquez et al. (Proc Natl Acad Sci USA, 2001, 98: 8403-8410) teach:

"Homologous recombination (HR) provides a precise mechanism for targeting defined modifications to genomes in living cells.

Thus, gene targeting is now a standard tool, however, does not mean that gene targeting is easy or that success is assured. Indeed, its application requires a certain persistence and effort that is not necessary, for example, in *Saccharomyces cerevisiae*.

The principal barrier to facile gene targeting in vertebrate cells is not the low frequency of HR, but rather the high frequency of random (nonhomologous) integration, which occurs in about one cell per  $10^2$  to  $10^4$  treated cells. For most cells, targeted recombinations are obscured by more than 1,000-fold higher frequency of random integrants."

In their review, Iida et al. (Plant Molecular Biology, 2005, 59: 205-219) teach:

"In higher plants, however, the overwhelming occurrence of the random integration of transgenes by non-homologous end-joining is the main obstacle to develop efficient gene targeting.

In addition to random integration mediated by non-homologous end-joining, the occurrence of aberrant recombination events associated with homologous gene targeting, called one-sided invasion and ectopic targeting, has also been reported.

There has been a single report describing the successful and reproducible targeting of the endogenous *Waxy* gene by homologous recombination without concomitant occurrence of ectopic event.

However, no article of another natural endogenous gene in rice has been published in the past 2 years since the first report, indicating that the progress of gene targeting in rice is apparently not so fast and we still need to accumulate more knowledge and know how to improve the procedures.”

Another unpredictable aspect is the silencing of the transcript encoding for a transcriptional repressor protein that controls the expression of the site-specific recombinase. Applicant asserts that the absence of the repressor protein would allow for the expression of the site-specific recombinase, which in turn would excise the pre-selected DNA sequence from the genome. However, this is not always true. Transcription is carried out by assemblies of transcription factors, and many of them are redundant in the cell. How could one of skill in the art know that inhibition of any repressor would result in efficient expression of the desired site-specific recombinase without undue experimentation? For example, Arnold et al. (Int J Dev Biol, 1966, 40: 345-353, Abstract) studies the role of the four myogenic regulating genes during mouse embryogenesis and found that Myf-5 and MyoD individually are not essential for the skeletal muscle development because they have redundant function.

Therefore, at the time the instant invention was made, the therapeutic gene targeting was a highly unpredictable art due to obstacles that continue to hinder gene targeting in general. Such obstacles include, for example, problems with chromosomal position effects that can lead to inefficient transgene expression and non-homologous integration that can lead to altered cellular phenotype.

One of skill in the art would need undue experimentation to know how to successfully modify the various cells and multi-cellular organisms, as broadly claimed, such that they would be able to selectively excise a pre-selected DNA sequence from their genome in response to the presence in the cells or multi-cellular organisms of polynucleic acid molecules having a region of predetermined sequence.

Applicant discloses that silencing of the repressor protein could be triggered, *in vitro* and *in vivo*, by a wide variety of stimuli, including synthetic siRNA, short RNA hairpin or long dsRNA. However, the use of short interfering nucleic to target genes is well known to be an unpredictable art. For example, Sledz et al. (Review, Blood, 2005, 106: 787-794) teaches:

“[E]ven following the recommended rules for siRNA design does not ensure effective silencing of the target genes. The efficacy of siRNA-mediated suppression of gene expression depends on a number of factors, including not only the chosen siRNA sequence but also the structure of the siRNA, and the receptiveness of the cell type to siRNA uptake. In addition, the half life of the target message and/or protein needs to be considered in order to achieve optimal silencing.

The use of RNAi for therapeutic purposes will depend on other factors as well. Although siRNAs are relatively stable in cell culture conditions, they require enhanced nuclease and thermodynamic stability when in circulation *in vivo*. Chemical modifications of siRNAs to enhance stability are being explored. While there are mixed opinions as to which type of modification will be most effective at enhancing stability without compromising target silencing, advances are being made towards the goal of making siRNAs suitable for therapeutic purposes.”

The problems of short interfering nucleic acids based therapies are well known in the art, particularly with regard to RNAi resistance, with regard to the inability to specifically deliver an effective concentration of a nucleic acid to a target cell, such that a target gene is inhibited to a degree necessary to result in the desired effect, and with regard to unpredicted nonspecific effects.

With respect to RNAi resistance, Woessmann et al. (Review, Rev. Clin. Exp. Hematol., 2003, 7: 270-291) teach:

"Due to the extreme sequence specificity of RNAi, a single point mutation in the targeted fusion site may abolish siRNA-mediated mRNA degradation of the oncogene, thus keeping the tumor resistant to RNAi. Secondly, mutations in proteins of the RNAi machinery, e.g. the argonaute proteins, could also render the tumor cells resistant to RNAi. Thirdly, an amplification of the fused oncogene, recently also demonstrated in BCR/ABL-positive leukemias after treatment with the tyrosine kinase inhibitor imatinib, may result in an inefficient fusion-gene suppression. Fourthly, RNAi could be antagonized by a mechanism called RNA editing.

RNA editing could antagonize RNAi through inhibition of the recognition of siRNA by the RNAi machinery, as has been seen in *Drosophila* cell-free extracts, or through insufficient base pairing between siRNA and target, inhibiting cleavage of the mRNA."

With respect to specific delivery, Opalinska et al. (Review, Nature Reviews Drug Discovery, 2002, vol 1, p. 503-514) state on page 511

"A newly developing approach for targeting mRNA is called post-transcriptional gene silencing, or RNA interference (RNAi)...The universality of this approach, and the types of gene that can be modified using this strategy in mammalian cells, remain unknown at this time.

[I]t is widely appreciated that the ability of nucleic-acid molecules to modify gene expression *in vivo* is quite variable, and therefore wanting in terms of reliability. Several issues have been implicated as a root cause of this problem, including molecule delivery to targeted cells and specific compartments within cells and identification of sequence that is accessible to hybridization in the genomic DNA or RNA....in mRNA, sequence accessibility is dictated by internal base pairing and the proteins that associate with the RNA in a living cell. Attempts to accurately predict the *in vivo* structure of RNA have been fraught with difficulty. Accordingly, mRNA targeting is a random process.

Another problem in this field is the limited ability to deliver nucleic acids into cells and have them reach their target. Without this ability, it is clear that even an appropriately targeted sequence is not likely to be efficient. As a general rule, oligonucleotides are taken up primarily through a combination of adsorptive and fluid-phase endocytosis. After internalization, confocal and electron microscopy studies have indicated that the bulk of the oligonucleotides enter the endosome-lysosome compartment, in which most of the material becomes either trapped or degraded."

With respect to the unpredicted nonspecific effects, Woessmann et al. teach:

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"[I]t is still an open question how specific the action of the siRNA really is. Recent findings suggest that that non-specific, so-called scrambled siRNA may produce translational inactivation by forming imperfect duplexes with bulging loops in the 3'UTR of unwanted genes. This inadvertent cross-hybridization may lead to subsequent downregulation of these genes, and in medical terms, the applicability of siRNA to modulate gene expression in human diseases, and in particular cancer, may be compromised. In addition to the possibility of cross-hybridization, siRNA could bind to various cellular proteins as does antisense DNA, resulting in a number of cellular effects not caused by Watson-Crick pairing.

Whether this finding may indeed seriously hamper the possibilities to develop gene-specific therapeutics on the basis of siRNA remains to be seen. To date, the prediction of the most effective but also specific siRNA for a particular target is not an easy task."

Therefore, at the time the instant invention was made, the use of short interfering nucleic acids was a highly unpredictable art due to obstacles that continue to hinder the therapeutic application of nucleic acids both *in vitro* and *in vivo* (whole organism) in general. Such obstacles include, for example, problems with delivery, target accessibility and the potential for unpredictable nonspecific effects.

Given these teachings, the one of skill in the art would not know *a priori* whether introduction of short interfering nucleic acids *in vivo* by the broadly disclosed methodologies of the instant invention, would result in the short interfering nucleic acids reaching the proper cell in a sufficient concentration and remaining for a sufficient time to provide successful inhibition of the transcriptional repressor. One of skill in the art would not know how to deliver short interfering nucleic acids to an organism or a cell in such a way that would ensure an amount sufficient to modify or inhibit expression of the target gene in the proper cell without unpredictable nonspecific effects.

**The Amount of Direction or Guidance/The Existence of Working Examples**

The specification does not provide the guidance or the working examples required to overcome the art-recognized unpredictability of using gene targeting applications in any cell or organism. The field of gene targeting does not provide that guidance, such that the skilled artisan would be able to practice the claimed invention.

### **Conclusion**

Thus, the specification is not enabling for the broad claims of (i) a method for selectively excising a pre-selected DNA sequence from a cellular genome (ii) a cell or multi-cellular organism wherein a pre-selected DNA sequence is excisable from the genome, (iii) a method for bringing the expression of a pre-selected gene in a cell under the control of a pre-selected promoter and (iv) a cell or multi-cellular organism wherein the expression of a pre-selected gene can be brought under the control of a pre-selected promoter.

In order to practice the claimed invention a number of variables would have to be optimized, including: (i) increasing the efficiency of homologous recombination, (ii) finding a way to avoid non-homologous recombination that could lead to inhibition of transgene expression due to chromosomal positional effects or altered cell phenotype, (iii) to determine whether the transcript encoding the repressor protein has overlapping or redundant functions and (iv) determine whether the selected cell or multi-cellular organism is amenable to the methodology to be used. Each one of these variables would have to be empirically determined for each particular case. Optimization of any single one of these steps is not routine and, when taken together, the amount of experimentation required becomes such that one of skill in the art could not practice the

invention commensurate in scope with the claims without undue, trial and error experimentation and therefore, claims 17-20, 22, 24, 25, 27, 29, 30, 32, and 36 are not enabled.


7. No claim is allowed. Claims 17-20, 22, 24, 25, 27, 29, 30, 32, and 36 are free of prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ileana Popa whose telephone number is 571-272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Ileana Popa

  
Primary Examiner  
AU 1633